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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,376	03/09/2001	Gary Van Nest	377882001700	8397

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

8/M

Office Action Summary	Application No.	Applicant(s)	
	09/802,376	NEST ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *12-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 56-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 2-13-04.

Claims 12-55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13. Claims 1-11, 56-66 have been examined on their merits as set forth in the Office action below.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2-13-04 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Applicant's arguments with respect to claims 1-11 and 56-66 have been considered but are moot in view of the new ground(s) of rejection set forth below.

Maintained Rejections

Claims 1, 2, 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Uhlen, for the reasons set forth in the Office action mailed 11-19-04.

Applicant's arguments filed 2-13-04 have been fully considered but they are not fully persuasive. Applicant argues that the instant invention is not anticipated by Uhlen because Uhlen teaches an immunomodulatory polynucleotide linked to the surface of a nonbiodegradable microcarrier for in vitro use, and not for administration to an individual or as a component of pharmaceutical composition. The instant rejection is drawn to the composition as it pertains to in vitro use, and not as drawn to the intended in vivo use of the composition. The instant specification is not enabling for the claimed compositions as compositions for treatment in an organism, as indicated below.

New Rejections and Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 56-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to pharmaceutical compositions comprising immunomodulatory polynucleotide/microcarrier complexes, comprising a polynucleotide linked to the

surface of a nonbiodegradable microcarrier. The composition and claims do not adequately describe the broad genus comprising polynucleotides linked to the surface of nonbiodegradable microcarriers for administration to an individual or as a component of a pharmaceutical composition. The specification lists various solid phase carriers, including polystyrene, silica, ferromagnetic and paramagnetic materials, as well as listing oil or lipid based microcarriers, including liposomes, complexes of cholesterol and phospholipid, or oil in water in oil emulsions. And the disclosure teaches such pharmaceutical compositions to specifically encompass non-encapsulating (e.g. linked) microparticles. But no adequate details are provided in the instant disclosure that concisely describe the genus comprising non-encapsulated microcarriers linked to polynucleotides for administration to an individual or as a component of a pharmaceutical composition. No description is provided for common structural attributes identifying the members of the genus comprising non-encapsulated (e.g. as opposed to encapsulated) polynucleotide-microcarriers that comprise liposomes, complexes of cholesterol and phospholipid or oil in water in oil emulsions. Nor has adequate description been provided for polynucleotide complexes with solid phase microcarriers for administration to an individual or as a component of a pharmaceutical composition. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics concisely identifying members of the proposed and very broad genus comprising polynucleotides linked to the surface of nonbiodegradable microcarriers for administration to an individual or as a

component of a pharmaceutical composition, and further whereby the liquid microcarrier-polynucleotide complexes within this genus do not comprise encapsulated polynucleotides, and since this genus is highly variant, the description provided for defining members of the genus from others is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species concisely describing the very broad genus claimed. Thus, applicant was not in possession of the claimed genus.

Claims 1-11 and 56-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro immunomodulation of mouse splenocytes and human PMN cells using the particularly described IMP/MC complexes of examples 1-4 of the instant specification, does not reasonably provide enablement for non-encapsulated microcarriers linked to polynucleotides for administration for treatment to an individual or as a component of a pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to immunomodulatory polynucleotide microcarrier complexes (IMP/MC) for administration to a subject for treatment or as a component of a pharmaceutical composition.

The state of the prior art and the predictability or unpredictability of the art. The prior art has shown that encapsulation of oligonucleotides enhances resistance of the oligonucleotides to nuclease degradation (see Gold et al, USPN 6,465,188, Oct. 15,

2002, at col. 4, line 58-col. 5, line 27; see also Kasid et al, USPN 6,559,129, May 6, 2003 at col. 21-23). Collins (USPN 6,355,267, Mar. 12, 2002) and Kasid et al (USPN 6,559,129, May 6, 2003) teach methods of encapsulating polynucleotides for in vitro and in vivo application. Kasid et teach, for instance, efficient encapsulation of nucleotides in cationic liposomes comprising DDAB:phosphatidylcholine and cholesterol most preferably at 1:3.2:1.6, respectively, whereby the lipids are first dissolved in solvent, evaporated to dryness, hydrated, then the nucleotide is added, and the solution is vigorously vortexed and sonicated, and the non-encapsulated oligonucleotides are then removed (see Kasid at col. 7-8, col. 10). Collins teaches the batch to batch variation in liposome preparation methods, leading to compositions comprising encapsulated and unencapsulated molecules associated with liposomes of varying lipid content (e.g. see Collins at col. 3 and 7). Collins also teaches efficient encapsulation of polynucleotides under conditions of strictly defined lipid compositions, comprising combining the lipids, drying and desiccating the lipid mixture, then hydrating at a temperature above the chain melting temperature of the distearoyl-phosphatidylcholine mixture, microfluidizing the sample and removing the unencapsulating material by ultracentrifugation (see Collins at col. 7-11). The art is silent, however, regarding the treatment effects of pharmaceutical compositions comprising non-encapsulated IMP/MC complexes in a subject, including solid phase and liquid phase microcarriers.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of generating non-encapsulated IMP/MC, whereby

the microcarrier is liquid phase. Applicants have not provided guidance in the specification toward of method of producing non-encapsulated IMP/MC compositions for administration in a subject or as a component for a pharmaceutical composition.

The specification teaches the generation of oil in water emulsion comprising an immunomodulatory oligonucleotide covalently linked to cholesterol, and further comprising homogenization of a mixture comprising squalene, sorbitan trioleate,and Tween80; the generation of a mixture comprising and immunomodulatory oligonucleotide and sulphate derivatized polycarbonate microparticles; the generation of immunomodulatory oligonucleotides covalently linked to (e.g. amino derivatized) polystyrene beads. The specification also teaches the immunomodulation of mouse spleen cells and human PMN cells in vitro following administration of these IMP/MC compositions. The specification fails to teach the administration of any IMP/MC to a subject for treatment. The specification fails to teach pharmaceutical compositions comprising adequate species representing the broad genus drawn to IMP/MC complexes, which IMP/MC comprise solid and non-encapsulated liquid microcarriers. One skilled in the art would not accept on its face the examples given in the specification of the in vitro immunomodulation of mouse splenocytes or human PMN cells, and using the particularly described IMP/MC of examples 1-4 of the instant specification, as being correlative or representative of the administration in a subject for treatment or of pharmaceutical compositions comprising any species encompassed within the broad genus comprising IMP/MC. The specification as filed fails to provide

any particular guidance which resolves the known unpredictability in the art associated with in vivo administration of the compositions claimed.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to immunomodulatory polynucleotide microcarrier complexes (IMP/MC) for administration to a subject for treatment or as a component of a pharmaceutical composition. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of the ability to administer to a subject an adequate representation of species encompassed by the genus comprising IMP/MC compositions to a subject, as well as the *de novo* determination of the ability to generate an adequate number of species of non-encapsulated IMP/MC compositions (comprising liquid microparticles), whereby non-encapsulation has been shown for such species. Since the specification fails to provide any particular guidance for the generation of an adequate number of species of IMP/MC for administration in a subject for treatment purposes, and fails to provide any particular guidance for the administration of this broad genus in a subject, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
4-15-04

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER